Allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: comparison of reduced-intensity conditioning versus myeloablative conditioning

Yundeok Kim

The Graduate School
Yonsei University
Department of Internal Medicine

Allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: comparison of reduced-intensity conditioning versus myeloabltive conditioning

A Dissertation
Submitted to the Department of Internal Medicine
And Graduate School of Yonsei University
In Partial fulfillment of the
Requirements for the degree of
Doctor of Internal Medicine

Yundeok Kim

December 2010

The certifies that the dissertation
of Yundeok Kim is approved

_____
Thesis supervisor: Yoo Hong Min

_____
Jin Seok Kim: Thesis Committee Member #1

_____
Hyun Soo Kim: Thesis Committee Member #2

The Graduate School
Yonsei University
December 2010

Contents

1. Introduction ……..1
2. Patients and methods
2.1. Patients ……...2
2.2. Conditioning regimens and GVHD prophylaxis……....2
2.3. Definitions ……..2
2.4. Statistical analyses ……2
3. Results
3.1. Patient characteristics ……4
3.2. Transplantation procedures ……4
3.3. Engraftment ……5
3.4. Graft-versus-host disease ……...5
3.5. Toxicites ……5
3.6. Response to transplant ……5
3.7. Clinical outcomes ……...5
4. Discussion …….....6
5. Reference ……...9
Abstract ……13
Table ……..14
Figure ……18

Introduction

The treatment outcome in adult acute lymphoblastic leukemia (ALL) has lagged behind that in childhood ALL, for which a long-term survival of well over 80% has been achieved. Adult ALL has a poor prognosis, with a 5-year overall survival (OS) rate of 39–50% despite aggressive chemotherapy [1–3] and only 15% for patients over 50 years of age [3]. As the high incidence of relapse is a main cause of treatment failure in adult ALL, optimal post-remission therapy, particularly the efficacy of allogeneic hematopoietic stem cell transplantation (alloHCT), is a critical issue [4–6]. According to the International ALL Trial (MRC UKALL XII/ECOG E2993) of chemotherapy versus autologous and allogeneic transplantation, alloHCT confers the greatest durable benefit for standard-risk adult patients and is more effective than either chemotherapy or autologous transplantation [7]. AlloHCT in first complete remission (CR1) has generally been reserved for those patients who present with poor risk features. In several phase II studies, patients with high-risk disease treated with alloHCT displayed a disease-free survival (DFS) longer than would have been predicted, particularly those with Philadelphia chromosome positive (Ph+) ALL [4–6]. However, AlloHCT is associated with significant morbidity and mortality because of the toxicity of the conditioning regimen, graft-versus-host disease (GVHD), and the immune deficiency state that accompanies the procedure. These risks are significantly increased with advanced age and concurrent medical problems, limiting myeloablative (MA) transplantation to younger patients in good medical condition.

Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-SCT) is a potential therapeutic approach for adults with high-risk ALL in remission who are ineligible for MA transplantation. This strategy decreases the risk of non-relapse mortality (NRM) while preserving the graft-versus-leukemic (GVL) effect. However, few studies have been conducted in patients with ALL, and all are retrospective [8–15]. Additionally, an evaluation of outcomes suggests that the GVL effect is more effective against myeloid malignancies such as acute and chronic myeloid leukemia, as well as malignancies of mature B cells such as low-grade non-Hodgkin’s lymphoma and multiple myeloma, but less so with a more undifferentiated B-cell disease such as pre-B ALL, particularly if not in remission [11,12]. Nevertheless, a few small studies have been reported to suggest that a role may well exist for RIC even in ALL. A retrospective analysis from the European Group for Blood and Marrow transplantation (EBMT) reported the outcome of 97 patients with ALL who received RIC and suggested that RIC may be effective in CR1 (2-year OS, 59%; treatment-related mortality (TRM), 18%) [15]. Considering the progress in adult ALL therapy and despite better disease control, high toxicity, and limited improvement in DFS in older adult patients, a detailed analysis is needed to determine whether RIC can improve the cure rate of older adults with ALL. Thus, we have conducted a direct comparison of the clinical outcomes of RIC and MA transplants in the treatment of patients exhibiting adult ALL.

Patients and methods

Patients

Between December 2001 and July 2009, a retrospective analysis was conducted on 49 ALL patients who received RIC (n = 14) and MA (n = 35) transplants at the Division of Hematology, the Yonsei University College of Medicine.

Conditioning regimen and GVHD prophylaxis

Transplantation procedures are shown in Table 3. Preparatory regimens included the following: in the RIC group, fludarabine (Flu)/busulfan (Bu) with (n = 3) or without (n =6) alemtuzumab, Flu/Bu with rabbit anti-thymocyte globulin (ATG) (n = 1), Flu/Bu with rituximab (n = 1), and Flu/melphalan (Mel) with (n = 2) or without (n = 1) another Flu-based regimen. In the MA group, 25 patients received total body irradiation (TBI) at 8 Gy and cyclophosphamide (Cy) with (n = 1) or without ATG (n = 24), and 10 patients received Bu/Cy. For GVHD prophylaxis, all patients who received cyclosporine (CSP) received transplants from unrelated donors or tacrolimus from related donors with a short course of intravenous bolus methotrexate as a post-transplantation immunosuppressant.

Definitions

The diagnosis of GVHD was based on clinical evidence with histologic confirmation whenever possible. Acute GVHD was graded from 0 to IV and was defined and classified according to the modified Glucksberg grading system [16]. Additionally, chronic GVHD was defined and classified according to the Seattle criteria [17]. Neutrophil engraftment was defined as having an absolute neutrophil count exceeding 0.5×10^9/L on the first of 3 consecutive days. Platelet engraftment was defined as having a platelet count of $>20 \times 10^9$/L on the first 7 consecutive days without transfusion support. TRM was defined as death without progression of underlying disease. OS was defined as the duration of survival between transplant and either death or last follow up. DFS was defined as the duration of survival after transplant without disease progression, relapse, or death. When ALL recurred before engraftment, the underlying disease was considered to have progressed on the day of transplant.

Statistical analyses

Patient characteristics in the RIC and MA groups were compared using Pearson's *chi*-squared test for discrete variables or the *t*-test for continuous variables. OS and DFS were the main end points of the present study. OS and DFS curves were constructed using Kaplan–Meier product-limit estimates [18]. Survival curves were compared using the log-rank test, taking the censored data into account. The list of features included was determined from a literature review that identified factors found to be associated with survival in patients treated with allogeneic transplantation. Factors associated by univariate analyses were subjected to multivariate analysis using backward stepwise proportional-hazard modeling. Values of $p < 0.05$ were considered to be statistically significant.

Statistical analyses were performed using SPSS 12.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The main clinical and biological characteristics at the time of diagnosis are displayed in Table 1. The median ages of the RIC and MA groups were 29 (range, 15–56 years) and 30 years (range, 15–46 years), respectively ($p = 0.646$). The median intervals between the diagnosis and transplantation of the RIC and MA groups were 164.5 (range, 76–565 days) and 156 days (range, 70~971 days), ($p = 0.372$). Twenty-three percent of patients in the RIC group required >28 days to achieve remission from the start of induction chemotherapy compared with 54.3% in the MA group ($p = 0.054$). Thirty-eight percent of patients in the RIC group had been diagnosed with high white blood cell (WBC) count ($\geq 30 \times 10^9$/L for B-precursor ALL and $\geq 100 \times 10^9$/L for T-precursor ALL) compared with 14.3% in the MA patient group ($p = 0.067$). Seven patients (50%) in the RIC group and 13 (37.1%) in the MA group demonstrated cytogenetic high-risk factors, including being Ph+ ($p = 0.165$) and Ph (four patients in the RIC group and 13 in the MA group, $p = 0.573$). All patients who were diagnosed as being Ph+ received remission induction chemotherapy with imatinib mesylate (Glivec®). The incidence of T-cell lineage and biphenotypic ALL in the RIC group (four patients (28.5%)) was not significantly different compared with the MA group (three patients (8.6%); $p = 0.209$).

Transplant procedures

Clinical and biological features presenting at transplantation are summarized in Table 2. Thirty-four patients (69.4%) were transplanted in CR1, seven (14.2%) in second complete remission (CR2), and eight (16.4%) in third complete remission (CR3) or beyond. The status at transplantation was not different between the RIC and MA groups ($p = 0.824$). All donor–recipient pairs were human leukocyte antigen (HLA) typed using high-resolution genotyping for both HLA class I (HLA-A, -B, and -C) and II (HLA-DRB1) antigens. In total, 12 patients (85.7%) in the RIC group and 33 (94.3%) in the MA group had full-matched sibling or unrelated donors, and the remaining two in each group (14.3% and 5.7%, respectively) were transplanted from ≥1-allele mismatched donors ($p = 0.327$). The median cell dose infused for the RIC and MA groups were 8.54×10^6 CD34+ cells/kg (range, 2.57–18.6×10^6 cells/kg) or 13.1×10^8 marrow-nucleated cells/kg (range, 3.58–18.26×10^8 cells/kg) and 6×10^6 CD34+ cells/Kg (range, 1.74–27.52×10^6 cells/kg) or 6.8×10^8 marrow-nucleated cells/kg (range, 1.32–14.8×10^8 cells/kg), respectively. In the RIC group, the stem cell source was peripheral blood in 13 patients (92.9%) and bone marrow in one patient (7.1%) compared with 25 patients (71.4%) and 10 patients (28.6%) in the MA group, respectively ($p = 0.108$).

Engraftment

All patients in the RIC and MA groups achieved neutrophil engraftment within a median interval of 13 days (range, 6–22 days) and 13 days (range, 4–23 days; $p = 0.906$), respectively. The time required to achieve platelet engraftment was 11 days (median; range, 0–17 days; two patients never experienced thrombocytopenia) in the RIC group compared with 12 days (median; range 3–33 days) in the MA group ($p = 0.496$).

Graft-versus-host disease

The incidences of grade II to IV acute GVHD (aGVHD) in the RIC and MA groups were comparable at 15.4% versus 25.7%, respectively ($p = 0.101$). The maximum ratings were grade II (n = 11), III (n = 13), or IV (n = 4). Additionally, the incidence of chronic GVHD (cGVHD) in patients who survived >100 days after transplantation was not significantly different between groups (45.7% versus 40%, respectively; $p = 0.783$).

Toxicities

Two patients in the MA group died because of severe hepatic veno-occlusive disease (VOD). However, in the RIC group, hepatic VOD did not occur ($p = 0.50$). Infection developed in seven (50%) patients in the RIC group and 27 (77.1%) patients in the MA group; this difference was not significant ($p = 0.065$). The frequencies of cytomegalovirus disease, fungal infection, and acute renal failure were similar in both groups ($p = 0.909$, $p = 0.375$, and $p = 0.150$, respectively) (Table 4).

Response to transplant

In all patients, minimal residual disease (MRD) was monitored using polymerase chain reaction (PCR) for short tandem repeats (STR) or variable number tandem repeats (VNTR) at day 14 or 21 following HCT (first chimerism). Subsequently, results were collected at day 28, month 3, and month 9 after HCT. At the first evaluation, 13 patients in the RIC group had achieved complete donor chimerism compared with 44 in the MA group ($p = 0.512$). Relapses were observed in 10 of 14 patients in the RIC group (nine (64.2%), complete chimerism; one (7.1%), mixed chimerism) and in 44 of 45 patients in the MA group (12 (34.3%), complete chimerism; $p = 0.055$).

Clinical outcomes

In the RIC group, the 1-year NRM and relapse rates were 0% ($p = 0.125$) and 64.3% ($p = 0.055$), respectively, compared with 34.8% and 34.3%, respectively, in the MA group. Although they were not statistically significant, we noted a trend toward higher NRM rates and lower relapse rates for the MA group. The most frequently encountered cause of NRM was infection, followed by GVHD. Relapse and death events were reported as days post HCT. The 3-year OS in the RIC and MA groups were 52% and 33%, respectively (Figure 1a; $p = 0.280$). The median duration of OS was 43.8 months (range, 43–44.3 months) in the RIC group and 55 months (range, 42–67.8 months) in the MA group. A significant difference in DFS was observed between the RIC and MA groups (Figure 1b).

The 3-year DFS rates were 25% in the RIC group and 68% in the MA group (p = 0.001). Univariate analysis for OS and DFS was conducted using the following factors: conditioning regimen, age, donor type, the interval from diagnosis to transplantation, disease status at transplantation, and karyotype at diagnosis (Table 5). Age, donor type, and the interval from diagnosis to transplantation were statistically significant with respect to OS ($p < 0.05$); however, none of these factors was found to significantly influence DFS. In our multivariate analysis using Cox regression hazard models, none of the factors used in the multivariate analyses had any significant influence on OS and DFS.

We divided patients into two age groups: ≤30 years and >30 years. According to Figure 2, OS was not significantly different between the RIC and MA groups for all patients (for patients ≤30 years old, 3-year OS = 59% vs. 78%, respectively (p = 0.892); for patients >30 years old, 3-year OS = 34% vs. 50%, respectively (p = 0.18)). However, the DFS in patients ≤30 years old in the MA group was superior to that in the RIC group (2-year DFS, 74% vs. 18%, respectively; p = 0.01). Conversely, the DFSs in the RIC and MA patient groups aged >30 years were 30% and 57%, respectively. No statistically significant difference was noted (p = 0.170; Figure 3).

Discussion

The rationale for RIC-SCT is that the toxicity of the conditioning regimen has been virtually removed, and the technique relies almost entirely on handling the GVL effect. The procedure is becoming established in acute myeloid leukemia (AML), multiple myeloma, and low-grade lymphoma [19]. Until now, few studies were conducted to evaluate the role of RIC-SCT in adult ALL [11–13]. ALL is relatively rare in adults, and its incidence increases dramatically with age. The cumulative incidence of ALL cases (per 100,000 in age-matched populations) triples in the >50-year-old age group compared with the 25- to 49-year-old age group [20]. Older patients have a very poor prognosis without HCT, but are generally ineligible for MA HCT because of high NRM, as demonstrated in the International ALL Trial [7]. The recently reported International ALL Trial comparing chemotherapy and allogeneic and autologous transplantation showed that alloHCT resulted in improved disease control in all adult patients with ALL, but with long-term benefit observed mostly in younger patients with lower-risk disease. Although the study clearly demonstrated better disease control, the overall benefit was undermined by the toxicity observed in older patients treated with the fully ablative TBI/etoposide regimen. Additionally, Larson [21] evaluated the outcomes for comparing chemotherapy with HCT. This trial has led to advocating early transplantation for nearly all patients, while others have cautioned a continued individual assessment. All agree that new approaches to reducing the toxicity of treatment in older patients are necessary. The development of RIC for ALL would give older patients transplant options and hope for disease control with fewer complications. Several studies have attempted to assess the efficacy of RIC-SCT for treatment of ALL in older patients.

In the present study, we compared the outcomes of 14 RIC with those of 35 MA transplants, all of which were conducted at a single institution during the same time span. No statistically significant difference was observed by age, sex, presenting WBC count, ALL type (B-lineage, T-lineage, or biphenotype), cytogenetic abnormalities, extramedullary involvement at presentation, and delayed time to CR achievement (time to first CR >28 days from the start of induction chemotherapy). Chimerism analysis is mandatory after RIC regimens for alloHSCT because the kinetics of lymphoid and myeloid engraftment may differ from those observed after traditional MA conditioning. In the present study, we analyzed chimerism at day 14 or 21 following HCT (first chimerism). Subsequently, results were collected at day 28, month 3, and month 9 after HCT. In the RIC and MA groups, most patients (n = 13 vs. n = 44, respectively) achieved complete chimerism at day 14 or day 21, respectively, with no significant difference between the groups ($p = 0.055$). Our data show that the OS of the RIC and MA groups at all ages was not different ($p = 0.280$), but the DFS between the two groups at all ages was statistically significant (3-year DFS rates, 25% vs. 68%, respectively; $p = 0.001$). We divided patients into two age groups: ≤30 years and >30 years. At younger ages (≤30 years) in the RIC and MA groups, the OS and DFS demonstrated similar trends compared with those at all ages (3-year OS, 59% vs. 78%, respectively; $p = 0.892$; 2-year DFS, 74% vs. 18%, respectively; $p = 0.01$). However, at older ages (>30 years), both the DFS and OS were not significantly different between the RIC and MA groups (30% vs. 57%, respectively; $p = 0.170$). Our data support recent reports that have compared the outcomes of RIC and MA transplants and have obtained results that generally favor RIC [22–24]. As anticipated, RIC with fludarabine-containing regimens was associated with a lower NRM than that observed after MA conditioning [25]. In our study, the 1-year NRM in the RIC group was 0%, compared with 34.8% in the MA group. Although it was not statistically significant ($p = 0.125$), we noted a trend toward higher NRM rates for the MA group. The development and severity of GVHD have been correlated with cytotoxic tissue injury and the resultant inflammatory cytokine milieu [26]. In our study, the incidence of both aGVHD (grade ≥II) and cGVHD (extensive) in the MA group (42.9% and 40%, respectively) was comparable to that in the RIC group (15.4% and 35.7%, respectively; $p = 0.101$ and $p = 0.783$, respectively). The low response rate in patients with ALL following donor leukocyte infusion (DLI) to treat post-transplant relapse has led to questions about the contribution of the GVL effect in preventing relapse in this disease. The GVL effect is derived from observations of a higher relapse rate after autologous or syngeneic HCT compared with alloHCT, lower incidence of relapse in patients who had GVHD, and increased relapse rate in recipients of T-cell-depleted marrow grafts. The most compelling argument for a strong GVL effect in ALL comes from both single-institution and registry data [30]. The occurrence of acute, chronic, or both forms of GVHD correlated with the best DFS. A study of 192 patients with ALL, most of whom were transplanted in second remission, showed a consistent decrease in relapse rates in patients who

develop aGVHD (grade ≥II) and cGVHD compared with patients who do not develop aGVHD and cGVHD [5]. Table 6 shows the relapse rate after HCT and its correlation with aGVHD ($p = 0.021$) and cGVHD ($p = 0.026$). Most, but not all, reports of infectious complications after RIC-SCT have demonstrated a lower incidence of bacterial infections after transplantation but a persistent risk of invasive fungal and cytomegalovirus (CMV) infections [26–28]. According to our results, incidences of bacterial infection and CMV infection were similar between the RIC and MA groups ($p = 0.065$ and $p = 0.909$, respectively). In other studies, patients who received RIC experienced less hepatic toxicity.This underscores the deleterious effects of cellular cytotoxicity and release of proinflammatory cytokines on hepatocytes caused by ablative regimens [29]. Similar results were reported in our study. No patient in the RIC group experienced hepatic VOD, in contrast to three patients in the MA group.

In conclusion, the present study suggests that RIC-SCT is a potential therapeutic approach for older patients (>30 years old) and those ineligible for MA transplantation, although all patients who experienced MA HCT demonstrate more favorable outcomes than those who experienced RIC. The poor outcome of older patients with ALL using either standard chemotherapy or transplant makes this an important consideration for treatment in those patients. However, the present study possesses several limitations because it was a retrospective study and its sample size was small. Thus, to validate these findings and those of other studies, we need to conduct a large, prospective clinical trial of RIC-SCT in patients with adult ALL, which will be the basis for prospective trials to determine whether RIC can improve the cure rate of older adults with ALL.

References

1. O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *J. Clin Oncol.* 2000; 18:547–561.
2. Larson RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P, Duggan D, Davey FR, Sobol RE, Frankel SR, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood.* 1995; 85:2025–37.
3. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, Lazarus HM, Franklin IM, Litzow MR, Ciobanu N, Prentice HG, Durrant J, Tallman MS, Goldstone AH; ECOG; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood.* 2005; 106:3760–7.
4. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, Kovacsovics T, Delannoy A, Fegueux N, Fenaux P, Stamatoullas A, Vernant JP, Tournilhac O, Buzyn A, Reman O, Charrin C, Boucheix C, Gabert J, Lhéritier V, Fiere D. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol.* 2004;15:22:4075–86.
5. Cornelissen JJ, Carston M, Kollman C, King R, Dekker AW, Löwenberg B, Anasetti C. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. *Blood*. 2001; 97:1572–7.
6. Hahn T, Wall D, Camitta B, Davies S, Dillon H, Gaynon P, Larson RA, Parsons S, Seidenfeld J, Weisdorf D, McCarthy PL Jr. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant.* 2006; 12:1–30.
7. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, Burnett AK, Chopra R, Wiernik PH, Foroni L, Paietta E, Litzow MR, Marks DI, Durrant J, McMillan A, Franklin IM, Luger S, Ciobanu N, Rowe JM. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood.* 2008; 15:111:1827–33.
8. Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis.

Cancer. 2006; 106:2657–63.
9. Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A, Mufti GJ, Kroger N, Zander AR, Heim D, Paluszewska M, Selleslag D, Steinerova K, Ljungman P, Cesaro S, Nihtinen A, Cordonnier C, Vazquez L, López-Duarte M, Lopez J, Cabrera R, Rovira M, Neuburger S, Cornely O, Hunter AE, Marr KA, Dornbusch HJ, Einsele H. Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood.* 2006; 108:2928–36.
10. Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A, Ben-Bassat I, Nagler A. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia.* 2006; 20(2):322–8.
11. Valcárcel D, Martino R, Caballero D, Martin J, Ferra C, Nieto JB, Sampol A, Bernal MT, Piñana JL, Vazquez L, Ribera JM, Besalduch J, Moraleda JM, Carrera D, Brunet MS, Perez-Simón JA, Sierra J. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. *J Clin Oncol.* 2008; 26:577–84.
12. Arnold R, Massenkeil G, Bornhäuser M, Ehninger G, Beelen DW, Fauser AA, Hegenbart U, Hertenstein B, Ho AD, Knauf W, Kolb HJ, Kolbe K, Sayer HG, Schwerdtfeger R, Wandt H, Hoelzer D. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. *Leukemia*. 2002; 16:2423–8.
13. Martino R, Giralt S, Caballero MD, Mackinnon S, Corradini P, Fernández-Avilés F, San Miguel J, Sierra J. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. *Haematologica.* 2003; 88:555–60.
14. Hamaki T, Kami M, Kanda Y, Yuji K, Inamoto Y, Kishi Y, Nakai K, Nakayama I, Murashige N, Abe Y, Ueda Y, Hino M, Inoue T, Ago H, Hidaka M, Hayashi T, Yamane T, Uoshima N, Miyakoshi S, Taniguchi S. Reduced-intensity stem-cell transplantation for adult acute lymphoblastic leukemia: a retrospective study of 33 patients. *Bone Marrow Transplant.* 2005; 35:549–56.
15. Mohty M, Labopin M, Tabrizzi R, Theorin N, Fauser AA, Rambaldi A, Maertens J, Slavin S, Majolino I, Nagler A, Blaise D, Rocha V; Acute Leukemia Working Party; European Group for Blood and Marrow Transplantation. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a

retrospective study from the European Group for Blood and Marrow Transplantation. *Haematologica.* 2008; 93:303–6.
16. Thomas ED, Storb R, Clift RA, Fefer A, Johnson L, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. Bone-marrow transplantation (second of two parts). *N Engl J Med*. 1975; 292:895–902.
17. Martin PJ. Biology of chronic graft-versus-host disease: implications for a future therapeutic approach. *Keio J Med.* 2008; 57(4):177–83.
18. Klein JP, Rizzo JD, Zhang MJ, Keiding N. Statistical methods for the analysis and presentation of the results of bone marrow transplants. Part 2: Regression modeling. *Bone Marrow Transplant.* 2001; 28:1001–11.
19. Stein A, Forman SJ. Allogeneic transplantation for ALL in adults. *Bone Marrow Transplant.* 2008; 41:439–46.
20. National Cancer Institute, Surveillance, Epidemiology, and End Results Program.
21. Larson RA. Allogeneic hematopoietic cell transplantation is not recommended for all adults with standard-risk acute lymphoblastic leukemia in first complete remission. *Biol Blood Marrow Transplant.* 2009; 15:11–6.
22. Alyea EP, Kim HT, Ho V, Cutler C, Gribben J, DeAngelo DJ, Lee SJ, Windawi S, Ritz J, Stone RM, Antin JH, Soiffer RJ. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood*. 2005; 15:105:1810–4.
23. Vela-Ojeda J, García-Ruiz Esparza MA, Tripp-Villanueva F, Ayala-Sánchez M, Delgado-Lamas JL, Garcés-Ruiz O, Rubio-Jurado B, Montiel-Cervantes L, Sánchez-Cortés E, García-Chavez J, Xolotl-Castillo M, Rosas-Cabral A, Salazar-Exaire D, Galindo-Rodríguez G, Aviña-Zubieta A. Allogeneic peripheral blood stem cell transplantation using reduced intensity versus myeloablative conditioning regimens for the treatment of leukemia. *Stem Cells Dev*. 2004; 13:571–9.
24. Le Blanc K, Remberger M, Uzunel M, Mattsson J, Barkholt L, Ringdén O. A comparison of nonmyeloablative and reduced-intensity conditioning for allogeneic stem-cell transplantation. *Transplantation*. 2004; 15:78:1014–20.
25. Mielcarek M, Martin PJ, Leisenring W, Flowers ME, Maloney DG, Sandmaier BM, Maris MB, Storb R. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood*. 2003; 15:102:756–62.
26. Junghanss C, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, Chauncey T, McSweeney PA, Little MT, Corey L, Storb R. Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. *Blood*. 2002; 15:99:1978–85.
27. Busca A, Locatelli F, Barbui A, Ghisetti V, Cirillo D, Serra R, Audisio E,

Falda M. Infectious complications following nonmyeloablative allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis.* 2003; 5(3):132–9.

28. Fukuda T, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, Martin PJ, Storb RF, Marr KA. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood.* 2003; 1:102:827–33.
29. Hogan WJ, Maris M, Storer B, Sandmaier BM, Maloney DG, Schoch HG, Woolfrey AE, Shulman HM, Storb R, McDonald GB. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. *Blood.* 2004; 1:103(1):78–84.
30. M.M. Horowitz, R.P. Gale and P.M. Sondel *et al.*, Graft-versus-leukemia reactions after bone marrow transplantation, *Blood*. 1990; 75:555–562

Abstract

Allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: comparison of reduced-intensity conditioning versus myeloablative conditioning

Allogeneic stem cell transplantation (SCT) is a curative treatment option for acute lymphoblastic leukemia (ALL). However, myeloablative (MA) SCT involves considerable toxicity, particularly in elderly patients, graft–versus-host disease (GVHD), and the immune deficiency state that accompanies the procedure. Reduced-intensity conditioning allogeneic stem cell transplantation (RIST) is being used for patients who are not able to endure MA conditioning because of the advanced age or other medical conditions. Also, RIST depends on graft-versus-tumor effects for their eradication of malignant cells. There have been fewer studies conducted in patients with ALL, and all are retrospective. In addition, an evaluation of outcomes suggests that the GVL effect is more effective against myeloid malignancies, such as acute and chronic myeloid leukemia, and malignancies of mature B cells, such as low-grade non-Hodgkin`s lymphoma and multiple myeloma, but less so with a more undifferentiated B-cell disease, such as pre-B ALL, especially if not in remission.
Nevertheless, a few small studies have been reported that suggested that there may well be a role for RIC-SCT even in ALL. Considering the progress in adult ALL therapy and despite better disease control, high toxicity and limited improvement in DFS in older adult patients, a detailed analysis is needed to determine if RIC can improve outcome of older adults with ALL. Therefore, we have conducted a direct comparison of the outcomes of RIC-SCT and myeloablative SCT in the treatment of patients exhibiting adults ALL.

,

Acute lymphoblastic leukemia, Allogeneic stem cell transplantation, Reduced-intensity conditioning, Myeloablative conditioning

Table 1. Clinical and biological characteristics of patients at diagnosis

	Reduced intensity (n = 14)	Myeloablative (n = 35)	*p*-value
Male : Female	9 : 5	20 : 15	0.646
Median age (range, year)	30 (12–56)	29 (15–46)	0.071
High WBC count (%)[a]	5 (38.5)	5 (14.3)	0.067
Immunophenotype (%)			
T-lineage B-lineage Biphenotype	3 (21.4) 10 (71.4) 1 (7.1)	1 (2.9) 32 (91.4) 2 (5.7)	0.209
Cytogenetics (%)			
Adverse[c] Normal Other	7 (50) 6 (42.9) 1 (7.1)	13 (37.1) 22 (62.9) 4 (11.4)	0.692
EM involvement (%)	4 (28.6)	4 (11.4)	0.147
Delayed time to CR (%)[b]	3 (23.1)	19 (54.3)	0.054

Abbreviations: WBC, white blood cell; EM, extramedullary; CR, complete remission.

[a] Presenting WBC counts ≥30 × 10^9/L for B-precursor ALL and ≥100 × 10^9/L for T-precursor ALL.

[b] Time to first CR >28 days from the start of induction chemotherapy.

[c] Included *t* (9;22), *t* (4;11), *t* (8;14), low hypodiploidy/near triploidy, and complex karyotype.

Table 2. Patient characteristics at transplantation

	Reduced intensity	Myeloablative	*p*-value
Disease status at HCT (%)			
CR1	9 (64.3)	25 (71.4)	0.824
CR2	2 (14.3)	5 (14.3)	
Other	3 (21.4)	5 (14.3)	
HLA			
Matched	12 (85.7)	33 (94.3)	0.327
Mismatched	2 (14.3)	2 (5.7)	
ABO			
Matched	9 (64.3)	23 (65.7)	0.925
Mismatched	5 (35.7)	12 (34.3)	
Relation with donor			
Related	6 (42.9)	19 (54.3)	0.470
Unrelated	8 (57.1)	16 (45.7)	
Stem cell source			
PB	13 (92.9)	25 (71.4)	0.108
BM	1 (7.1)	10 (28.6)	
CMV serotype (donor to recipient)			
Pos to Pos	12 (85.7)	33 (94.3)	0.327
Pos to Neg	2 (14.3)	2 (5.7)	
Median CD34+ cells ($\times 10^6$/kg, median, range)	8.5 (2.5~18.6)	6.5 (1.7~27.5)	0.514
Total nucleated cells ($\times 10^8$/kg, median, range)	13.1 (3.5~18.2)	6.8 (1.3~14.8)	0.868
Neutrophil engraftment (days, median, range)[b]	13 (6~22)	13 (4–23)	0.906
Platelet engraftment (days, median, range)[b]	11 (0~17)	12 (3~33)	0.496

Abbreviations: HCT, hematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; HLA, human leukocyte antigen; PB, peripheral blood; BM, bone marrow; CMV, cytomegalovirus; Neg, negative; Pos, positive.

[a] Interval from the start of induction chemotherapy to the date of transplantation.

[b] Neutrophil $>5 \times 10^9$/L, platelet $>20 \times 10^9$/L.

Table 3. Conditioning regimens

Conditioning regimen	No. of patients
Reduced intensity	14
Fludarabine (30 mg/m^2/day I.V. for 30 min; D-7 to D-3) + Busulfan (3.2 mg/kg/day I.V. for 30 min; D-5 to D-2)	11
Fludarabine (25 mg/m^2/day I.V. for 30 min; D-6 to D-3) + Melphalan (70 mg/kg/day I.V. for 30 min; D-3 to D-2)	3
Myeloablative	35
TBI (8 Gy for D-8 to D-5) + Cyclophosphamide (60 mg/kg/day I.V. for 1 hr, D-3 to D-2)	24
Busulphan (3.2 mg/kg/day I.V. for 2 h, D-7 to D-4) + Cyclophosphamide (60 mg/kg/day I.V. for 1 h, D-3 to D-2)	10

Abbreviations: I.V., intravenous; TBI, total body irradiation.

Table 4. Toxicity and complication profile of the patients

	Reduced intensity	Myeloablative	*p*-value
Acute GVHD (grade ≥II)	2 (15.4)	9 (42.9)	0.101
Chronic GVHD (extended)	5 (35.7)	14 (40)	0.783
Hepatic VOD	0	3 (8.6)	0.263
Infection	7 (50)	27 (77.1)	0.065
CMV disease	3 (14.3)	7 (20)	0.909
	3 (21.4)	13 (37.1)	0.294
Causes of death Relapse/disease progression Infection GVHD Other TRM	 4 (28.6) 5 (35.7) 2 (14.3) 0	 2 (5.7) 9 (25.7) 4 (11.4) 5 (14.3)	0.895

Abbreviations: GVHD, graft-versus-host disease; VOD, veno-occlusive disease; CMV, cytomegalovirus; TRM, treatment-related mortality.

Table 5. Univariate proportional hazard analysis on OS and DFS

	OS	DFS
	p-value	*p*-value
Age (≤30 vs. >30 years)	0.039	0.135
Karyotype (adverse vs. other)	0.900	0.170
Conditioning (RIC vs. MA)	0.157	0.263
Donor type (related vs. unrelated) (matched vs. mismatched)	 0.046 0.045	 0.082 0.789
Interval from Dx to HCT (<1 vs. ≥1 year)	 0.198	 0.412
Disease status at transplant (CR1 vs. other)	 0.010	 0.201

Abbreviations: RIC, reduced-intensity conditioning, MA, myeloablative; Dx, diagnosis; HCT, hematopoietic stem cell transplantation; CR1, first complete remission; OS, overall survival; DFS, disease-free survival.

Table 6. Relapse after transplantation

	No. of relapsed patients (%)	No. of non-relapsed patients (%)	*p*-value
Acute GVHD (grade ≥II)	8 (28.6)	13 (61.9)	0.021
Chronic GVHD (extended)	6 (26.1)	15 (57.7)	0.026

Abbreviations: GVHD, graft-versus-host disease.

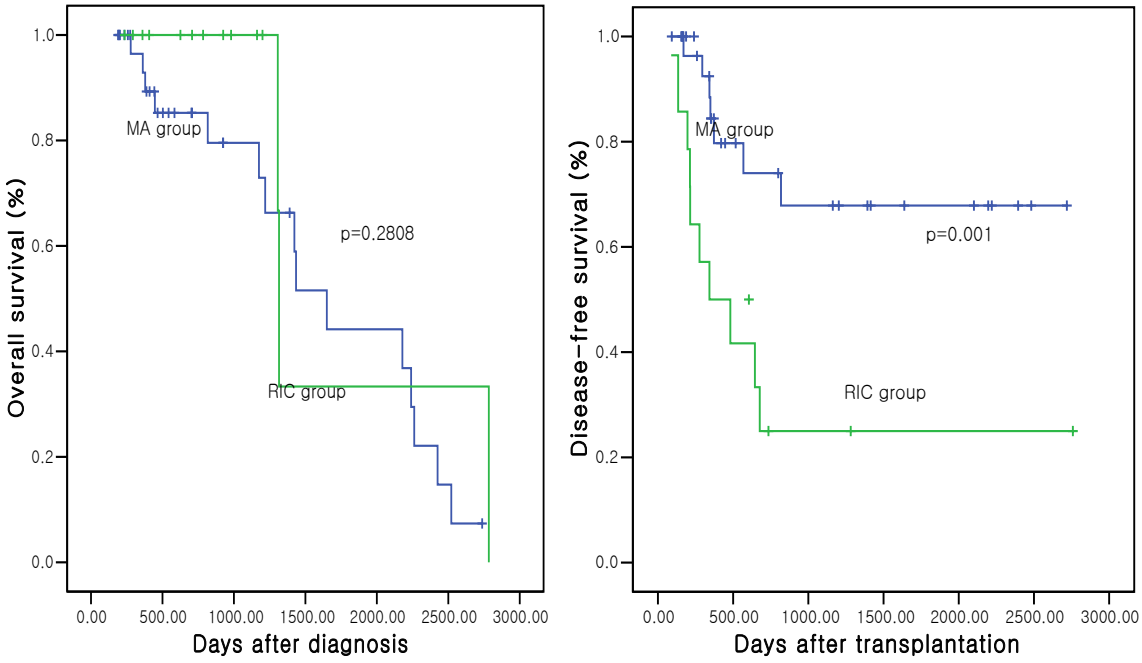

Fig. 1. Overall survival (a) and disease-free survival (b) in all patients

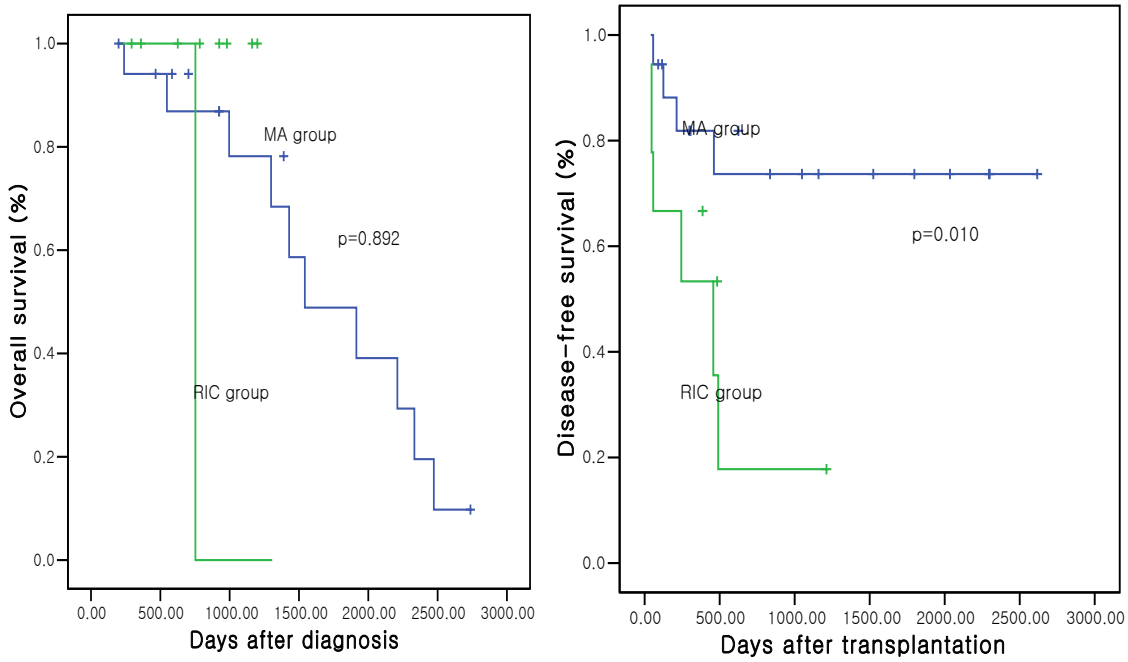

Fig. 2. Overall survival (a) and disease-free survival (b) in patients ≤30 years old

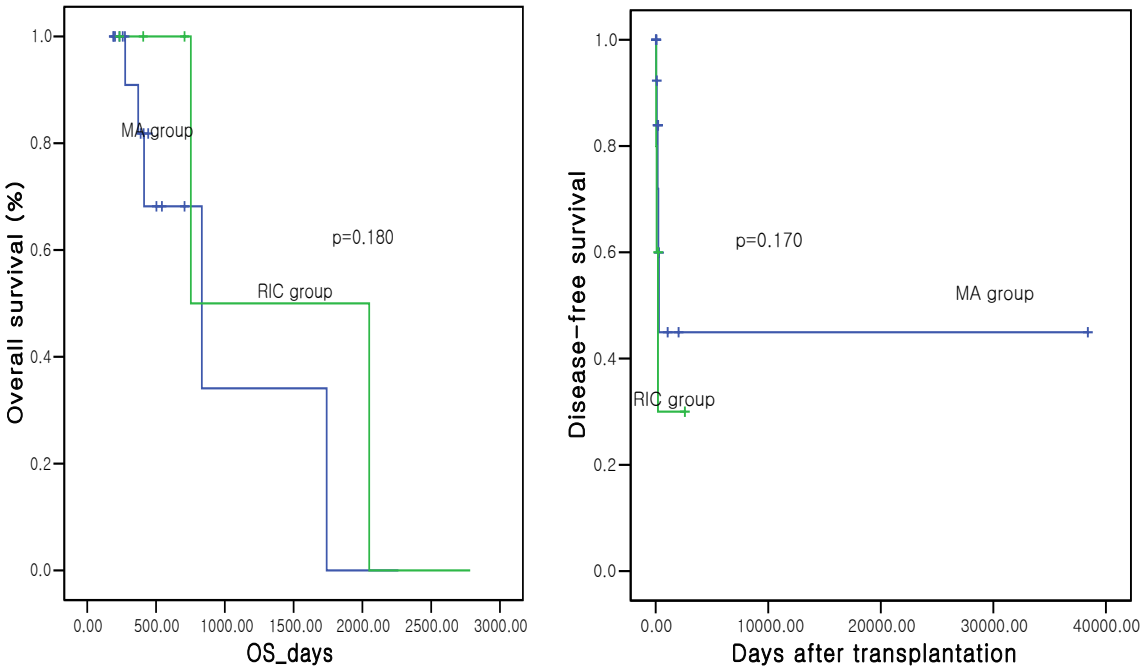

Fig. 3. Overall survival (a) and disease-free survival b) in patients >30 years old